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First Author is a: Investigator**First Author is a member of:** American Society for Biochemistry and Molecular Biology**First Author Degree:** PhD, DSc, or equivalent**Presentation Preference:** Oral**Sponsor:** Narendra Kumar**Sponsor Phone:** 3612210743

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Janus Kinase 3 modulates the tolerogenic immunology of liver through Kupffer cells.

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Background: Janus kinase 3 (Jak3) is a non-receptor protein kinase involved in a diverse array of processes like differentiation, development, cell-growth and hematopoietic signaling cascades. We have previously shown that loss of Jak3 exacerbates symptoms of inflammatory bowel disease (IBD) in a murine model of ulcerative colitis. The compromised intestinal barrier functions in ulcerative colitis have been shown to lead to systemic chronic low grade inflammation and subsequent hepatic disease. In this report, we investigated the tissue-specific role of Jak3 in maintaining hepatic homeostasis during ulcerative colitis.

Methods: In order to test our hypothesis, we used a global Jak3 KO (*Jak3^{-/-}*) mice model and compared its effect with either the intestinal epithelial specific Jak3 KO (Int Jak3 KO) mice or immune cell specific Jak3 KO (Imm Jak3 KO) mice. These mice were treated with 2.5% 40 kda DSS in our study. The organs were collected at the end of the study period under aseptic conditions and analyzed using a combination of flowcytometric, confocal microscopy, and western analysis techniques.

Results: Our results show increased susceptibility to colitis in DSS-treated *Jak3^{-/-}* mice. They also show a high-degree of association between the disease scores and hepatic inflammation in Imm Jak3 KO mice, indicating a prominent role of hematopoietic Jak3 in maintaining hepatic immunological homeostasis. A differential flowcytometric assay showed an increased influx of monocytes, but reduced differentiation of residential kupffer cells in imm Jak3 KO mice compared to its floxed control during ulcerative colitis. Further, the same group of mice also showed an increased TLR-4 expression and higher IL-6, IL-17 and Tnf- α as compared to the control mice. Together, these results confirm the lack of Jak3 in immune cells leads to a compromise in the activation of kupffer cells coupled with increased extravasation of the circulating monocytes into the liver. This could lead to liver disease and inflammation in ulcerative colitis. In addition, we also found an increased Th₁₇ effector function and simultaneous suppression of T_{reg} cell proliferation in the absence of immune cell Jak3, when compared to its control mice, on treatment with DSS.

Conclusion: Collectively, these results indicate that Jak3 plays a major role in regulating the macrophage based tolerogenic immunology of the hepatic system.

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